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Maximum Contaminant Level Goals for Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonic Acid (PFOS) in Drinking Water

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Prepared by**:**

U.S. Environmental Protection Agency
Office of Water (4304T)
Health and Ecological Criteria Division
Washington, DC 20460

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Abbreviations and Acronyms

CalEPA	California Environmental Protection Agency
CAR	constitutive androstane receptor
DNA	deoxyribonucleic acid
DWI-BW	body weight-adjusted drinking water intake
EPA	U.S. Environmental Protection Agency
ER	estrogen receptor
HAWC	Health Assessment Workplace Collaboration
HERO	Health and Environmental Research Online
HESD	health effects support documents
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
LCT	Leydig cell tumors
MCLG	Maximum Contaminant Level Goal
MOA	mode of action
NCI	National Cancer Institute
NHANES	National Health and Nutrition Examination Survey
NJDWQI	New Jersey Drinking Water Quality Institute
NPDWR	National Primary Drinking Water Regulation
NTP	National Toxicology Program
OCHP	Office of Children's Health Protection
OLEM	Office of Land and Emergency Management
OR	odds ratio
ORD	Office of Research and Development
OSCPP	Office of Chemical Safety and Pollution Prevention
OW	Office of Water
PACT	pancreatic acinar cell tumors
PECO	Population, Exposure, Comparator, and Outcome
PFAS	per- and polyfluoroalkyl substances
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonic acid
PLCO	prostate, lung, colorectal, and ovarian
POD	point of departure
PPAR	peroxisome proliferator-activated receptor
PPRTV	Provisional Peer Reviewed Toxicity Value
PWS	public water systems
PXR	pregnane X receptor
QA	quality assurance
RCC	renal cell carcinoma
RfD	reference dose
RSC	relative source contribution
SAB	Science Advisory Board
SDWA	Safe Drinking Water Act
SEM	systematic evidence map
UCMR	Unregulated Contaminant Monitoring Rule

1 Introduction

1.1 Background and Purpose

Section 1412(a)(3) of the Safe Drinking Water Act (SDWA) requires the Administrator of the U.S. Environmental Protection Agency (EPA) to finalize a Maximum Contaminant Level Goal (MCLG) simultaneously with the publication of a National Primary Drinking Water Regulation (NPDWR). The MCLG is set, as defined in Section 1412(b)(4)(A), at "the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." Consistent with SDWA 1412(b)(3)(C)(i)(V), in developing the MCLG, the EPA considers "the effects of the contaminant on the general population and on groups within the general population such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population." Other factors considered in determining MCLGs for drinking water contaminants include health effects data, toxicity values, cancer classifications, and potential sources of exposure other than drinking water. MCLGs are not regulatory levels and are not enforceable.

The purpose of this document is to provide a summary of the relevant health effects information, and to describe the derivation of the EPA's final individual MCLGs for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) used in the Per- and Polyfluoroalkyl Substances (PFAS) NPDWR (USEPA, 2024f). The individual MCLGs are based on the final toxicity assessments for PFOA or PFOS, which were developed and finalized to support the PFAS NPDWR (USEPA, 2024d, e). The toxicity assessments underwent both external peer review through the EPA Science Advisory Board (USEPA OOW, 2023) and public comment (USEPA, 2024c). This document summarizes the key elements (e.g., cancer classifications) that the agency used as the basis for determining the individual MCLGs for PFOA and PFOS and provides the final MCLGs for PFOA and PFOS used in the PFAS NPDWR. It is not intended to be an exhaustive description of all health effects information or quantitative analyses provided in the final human health toxicity assessments (USEPA, 2024d, e), nor is it a drinking water health advisory.

1.2 Occurrence of PFOA and PFOS in Drinking Water

The EPA uses the Unregulated Contaminant Monitoring Rule (UCMR) to collect data for contaminants that are suspected to be present in drinking water and do not have health-based standards set under the SDWA. Under the UCMR, drinking water is monitored from public water systems (PWSs), specifically community water systems and non-transient non-community water systems. UCMR improves the EPA's understanding of the frequency and concentrations of contaminants of concern occurring in the nation's drinking water systems. The first four UCMRs collected data from a census of large water systems (serving more than 10,000 people) and from a statistically representative sample of small water systems (serving 10,000 or fewer people). UCMR 3 monitoring occurred between 2013 and 2015 and is currently the most comprehensive nationally representative finished water dataset for PFOA and PFOS (USEPA, 2024f, g). Under UCMR 3, 36,972 samples from 4,920 PWSs were analyzed. PFOA was found above the UCMR 3 minimum reporting level (20 ng/L) in 379 samples at 117 systems serving a population of

approximately 7.6 million people located in 28 states, Tribes, or U.S. territories (USEPA, 2024f, g). PFOS was found in 292 samples at 95 systems above the UCMR 3 minimum reporting level (40 ng/L) (USEPA, 2024f, g). These systems serve a population of approximately 10.4 million people located in 28 states, Tribes, or U.S. territories (USEPA, 2024f, g).

More recent state data were collected using newer EPA-approved analytical methods and some state results reflect lower reporting limits than those in the UCMR 3. State data are available from 32 states: Alabama, Arizona, California, Colorado, Delaware, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Maine, Maryland, Massachusetts, Michigan, Minnesota, Missouri, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oregon, Pennsylvania, South Carolina, Tennessee, Vermont, Virginia, West Virginia, and Wisconsin (USEPA, 2024f, g). State results show continued occurrence of PFOA and PFOS in multiple geographic locations. These data also show PFOA and PFOS occurrence at lower concentrations and significantly greater frequencies than were measured under the UCMR 3, likely because the more recent monitoring was able to rely on more sensitive analytical methods (USEPA, 2024f, g). More than one-third of states that conducted non-targeted monitoring detected PFOA and/or PFOS at more than 25% of systems (USEPA, 2024f, g). Among the detections, PFOA concentrations ranged from 0.21 to 650 ng/L with a range of median concentrations from 1.27 to 5.61 ng/L, and PFOS concentrations ranged from 0.24 to 650 ng/L with a range of median concentrations from 1.21 to 12.1 ng/L (USEPA, 2024f, g). Monitoring data for PFOA and PFOS from states that conducted targeted monitoring efforts, including 15 states, demonstrate results consistent with the non-targeted state monitoring. Within the 20 states that conducted non-targeted monitoring there are 1,260 systems with results above 4.0 ng/L and 1,577 systems with results above 4.0 ng/L (USEPA, 2024f, g). These systems serve populations of 12.5 and 14.4 million people, respectively. Monitoring data for PFOA and PFOS from states that conducted targeted sampling efforts showed additional systems exceeding 4 ng/L (USEPA, 2024f, g).

Finally, the fifth UCMR (UCMR 5) was published in December 2021 and requires sample collection and analysis for 29 PFAS, including PFOA and PFOS, between January 2023 and December 2025 using drinking water analytical methods developed by the EPA (USEPA, 2021b). The UCMR 5 defined the minimum reporting level at 4 ng/L for PFOA and PFOS using EPA Method 533 which is lower than the 20 and 40 ng/L, respectively, used in UCMR 3 with EPA Method 537 (USEPA, 2021b). Therefore, UCMR 5 will be able to provide nationally representative occurrence data for PFOA and PFOS at lower detection concentrations. While the complete UCMR 5 dataset is not currently available, the small subset of data released (7% of the total results that the EPA expects to receive) as of July 2023 is consistent with the results of UCMR 3 and the state data described above (USEPA, 2024f, g).

2 Methods

2.1 Approach for Deriving an MCLG

The MCLG is set, as defined in Section 1412(b)(4)(A), at "the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." Consistent with SDWA Section 1412(b)(3)(C)(i)(V), in developing the MCLG, the EPA considers "the effects of the contaminant on the general population and on groups within the general population such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population." To establish the MCLG, the EPA assesses the available data examining cancer and noncancer health effects associated with oral exposure to the contaminant. For known or likely linear carcinogenic contaminants, where there is a proportional relationship between dose and carcinogenicity at low concentrations or where there is insufficient information to determine that a carcinogen has a threshold dose below which no carcinogenic effects have been observed, the EPA has a long-standing practice of establishing the MCLG at zero (see USEPA, (2001, 2000b, 1998); see S. Rep. No. 169, 104th Cong., 1st Sess. (1995) at 3). This is called the linear default extrapolation approach and ensures that the MCLG is set at a level where there are no anticipated adverse health effects, allowing for an adequate margin of safety. For nonlinear carcinogenic contaminants, contaminants that are designated as *Suggestive Human Carcinogens* (USEPA, 2005), and non-carcinogenic contaminants, the EPA typically establishes the MCLG based on a noncancer RfD. An RfD is an estimate of a daily exposure to the human population (including sensitive populations) that is likely to be without an appreciable risk of deleterious effects during a lifetime. A nonlinear carcinogen is a chemical agent for which the associated cancer response does not increase in direct proportion to the exposure level and for which there is scientific evidence demonstrating a threshold level of exposure below which there is no appreciable cancer risk.

A noncancer MCLG is designed to be protective of noncancer effects over a lifetime of exposure with an adequate margin of safety, including for sensitive populations and lifestages, consistent with SDWA 1412(b)(3)(C)(i)(V) and 1412(b)(4)(A). The inputs for a noncancer MCLG include an oral noncancer toxicity value, body weight-adjusted drinking water intake (DWI-BW), and a relative source contribution (RSC), as presented in the equation below:

$$\boldsymbol{MCLG} = \left(\frac{Oral\ RfD}{DWI\text{-}BW}\right) * RSC$$

Where:

RfD = chronic reference dose – an estimate (with uncertainty spanning perhaps an order of magnitude) of daily oral exposure of the human population to a substance that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is equal to a point of departure (POD) human equivalence dose (HED) (POD_{HED}) divided by a composite uncertainty factor.

DWI-BW = An exposure factor for the 90th percentile body weight-adjusted drinking water intake value for the identified population or lifestage, in units of liters of water

consumed per kilogram body weight per day (L/kg bw-day). The DWI-BW considers both direct and indirect consumption of drinking water (indirect water consumption encompasses water added in the preparation of foods or beverages, such as tea or coffee). Chapter 3 of the EPA's *Exposure Factors Handbook* (USEPA, 2019) provides the most up-to-date DWI-BWs for various populations or lifestages within the U.S. general population for which there are publicly available, peer-reviewed data such as from the National Health and Nutrition Examination Survey (NHANES).

RSC = relative source contribution – the percentage of total exposure attributed to drinking water sources (USEPA, 2000a), with the remainder of the exposure allocated to all other routes or sources. The purpose of the RSC is to ensure that the level of a contaminant (e.g., MCLG value), when combined with other identified sources of exposure common to the population and contaminant of concern, will not result in exposures that exceed the RfD. The RSC is derived by applying the Exposure Decision Tree approach published in EPA's *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health* (USEPA, 2000a).

Because the cancer classification of the chemical determines which approach that the EPA used to derive the MCLGs, the EPA summarizes the carcinogenic data evaluated for cancer classification selection below. The EPA followed a transparent systematic review process to evaluate the best available science and to determine the weight of evidence for carcinogenicity and the cancer classifications for PFOA and PFOS, individually, according to agency guidance (USEPA, 2005). Following this guidance, and as detailed below, the EPA determined that PFOA and PFOS are each classified as *Likely to Be Carcinogenic to Humans* based on sufficient evidence of carcinogenicity in the available human and animal studies. The EPA also determined that a linear default extrapolation approach is appropriate for PFOA and PFOS as there is no available evidence demonstrating a threshold level of exposure below which there is no appreciable cancer risk for either compound (USEPA, 2016c, 2005). Therefore, the EPA concluded that there is no known threshold for carcinogenicity. Because of these cancer conclusions the noncancer health effects that the EPA identified as hazards in the draft toxicity assessments (e.g., decreased immune response in children, increased serum alanine aminotransferase (ALT), decreased birth weight, increased serum total cholesterol) are not the basis for the final MCLGs and are not, therefore, described in this document. Details related to the noncancer effects associated with PFOA and PFOS can be found in the final human health toxicity assessments for PFOA and PFOS (USEPA, 2024d, e).

2.2 Summary of the EPA's Systematic Review of the Health Effects Data for PFOA and PFOS

The EPA conducted the systematic review of the cancer health effects data for PFOA and PFOS consistent with the methods described in the *EPA ORD Staff Handbook for Developing IRIS Assessments* (USEPA, 2022a) (hereafter referred to as the Integrated Risk Information System (IRIS) Handbook) and a companion publication (Thayer et al., 2022). The agency's systematic review incorporated and considered studies that are consistent with the SDWA mandate to "use (i) the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices; and (ii) data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies use of the data)" (SDWA(b)(3)(A)). Full details of the systematic review methodology can be found in Appendix A of the toxicity assessments for PFOA and PFOS (USEPA, 2024a, b).

2.2.1 Literature Search

The EPA assembled an inventory of epidemiological, animal toxicological, and mechanistic studies based on three data sources: 1) literature published from 2014 through 2019 and then updated throughout the course of this review (i.e., through February 3, 2022) identified via literature searches of a variety of publicly available scientific literature databases; 2) literature identified via other sources (e.g., searches of the gray literature and studies shared with the EPA by the Science Advisory Board (SAB)); and 3) literature identified in the EPA's 2016 health effects support documents (HESDs) for PFOA and PFOS (USEPA, 2016a, b). Additionally, the EPA identified studies from a supplemental literature search conducted in February 2023 as well as studies received through public comments and included those studies that were deemed to have the potential to quantitatively affect the final toxicity values (i.e., RfDs and cancer slope factors) or MCLGs for PFOA or PFOS in a significant way (i.e., by an order of magnitude or more). For additional details related to the literature included, please refer to Sections 2.1 and 3.1 in the final human health toxicity assessments USEPA (2024e); and USEPA (2024b) as well as Section A.1.5 in USEPA (2024d) and USEPA (2024a).

2.2.2 Literature Screening

The EPA used populations, exposures, comparators, and outcomes (PECO) criteria to screen all of the literature identified from the literature sources outlined above in order to prioritize the dose-response studies for dose-response assessment and to identify studies containing supplemental information such as mechanistic studies that could inform the mode of action analysis.

Consistent with protocols outlined in the IRIS Handbook (USEPA, 2022b), studies identified in the literature searches and stored in HERO were imported into the Swift-Review software platform and the software was subsequently used to identify those studies most likely to be relevant to human health risk assessment. Studies captured then underwent title and abstract screening by at least two reviewers using screening tools consistent with the IRIS Handbook (USEPA (2022b); DistillerSR or SWIFT ActiveScreener software), and studies that passed this screening underwent full-text review. Dose-response studies that met PECO inclusion criteria following both title and abstract screening and full-text review underwent study quality evaluation as described below. Studies tagged as supplemental and containing potentially

relevant mechanistic data following title and abstract and full-text level screening underwent further screening using mechanistic-specific PECO criteria, and those deemed relevant underwent light data extraction of key study elements (e.g., mechanistic endpoints evaluated, dose levels tested). Supplemental studies that were identified as mechanistic via screening did not undergo study quality evaluation. For additional details related to literature screening, please refer to Section A.1.8 in the *Final Human Health Toxicity Assessment for PFOA* (USEPA, 2024e) and PFOS (USEPA, 2024d).

2.2.3 Study Quality Evaluation for Epidemiological Studies and Animal Toxicological Studies

For study quality evaluation of the PECO-relevant human epidemiological and animal toxicological studies identified for cancer, two or more quality assurance (QA) reviewers, working independently, assigned ratings about the reliability of study results (*good, adequate, deficient* (or *"not reported"*), or *critically deficient*) for different evaluation domains consistent with the IRIS Handbook (USEPA, 2022b). These study quality evaluation domains are listed below and details about the domains, including prompting questions and suggested considerations, are described in Section A.1.9 in the *Final Human Health Toxicity Assessment for PFOA* (USEPA, 2024e) and PFOS (USEPA, 2024d).

- Epidemiological study quality evaluation domains: participant selection; exposure measurement criteria; outcome ascertainment; potential confounding; analysis; selective reporting; and study sensitivity.
- Animal toxicological study quality evaluation domains: reporting; allocation; observational bias/blinding; confounding/variable control; reporting and attrition bias; chemical administration and characterization; exposure timing, frequency, and duration; endpoint sensitivity and specificity; and results presentation.

The independent reviewers performed study evaluations using a structured platform housed within the EPA's Health Assessment Workplace Collaboration (HAWC; https://hawcproject.org/). Once the individual domains were rated, reviewers independently evaluated the identified strengths and limitations of each study to reach an overall classification on study confidence of *high, medium, low*, or *uninformative* for each relevant endpoint evaluated in the study. A study can be given an overall *mixed* confidence classification if different PECO-relevant endpoints within the study receive different confidence ratings (e.g., *medium* and *low* confidence classifications). All study evaluations are publicly available in HAWC at https://hawc.epa.gov/study/assessment/100500248/. For additional details related to study evaluation, please refer to Section A.1.9 in the *Final Human Health Toxicity Assessment for PFOA* (USEPA, 2024e) and PFOS (USEPA, 2024d).

2.2.4 Data Extraction

Data extraction was conducted for all relevant human epidemiological and animal toxicological studies determined to be of *medium* and *high* confidence based on study quality evaluation. Data were also extracted from *low* confidence epidemiological studies when data were limited for a health outcome or when there was a notable effect, consistent with the IRIS Handbook (USEPA, 2022b). Data extracted from *low* confidence studies was considered qualitatively only. Studies evaluated as being *uninformative* were not considered further and therefore did not undergo data

extraction. All health endpoints were considered for extraction, regardless of the magnitude of effect or statistical significance of the response relative to the control group. The level of detail in data extractions for different endpoints within a study could differ based on how the data were presented for each outcome (i.e., ranging from a narrative to a full extraction of dose-response effect size information).

Extractions were conducted using DistillerSR for epidemiological studies and HAWC for animal toxicological studies. An initial reviewer conducted the extraction, followed by an independent QA review by a second reviewer who confirmed accuracy and edited/corrected the extracted data as needed. Discrepancies in data extraction were resolved by discussion and confirmation within the extraction team.

Data extracted from epidemiology studies included population, study design, year of data collection, exposure measurement, and quantitative analyses of the data from statistical models. Results extracted from statistical models performed in the studies included the health effect category, endpoint measured, sample size, description of effect estimate, covariates, and model comments. Data extracted from animal toxicological studies included information on the experimental design and exposure duration, species and number of animals tested, dosing regime, and endpoints measured. For additional details related to data extraction, please refer to Sections A.1.10 and A.1.11 in the *Final Human Health Toxicity Assessment for PFOA* (USEPA, 2024e) and PFOS (USEPA, 2024d).

2.3 Approach for Determining the Cancer Classification

In accordance with the EPA's 2005 *Guidelines for Carcinogen Risk Assessment*, a descriptive weight of evidence expert judgment is made, based on all available animal, human, and mechanistic data, as to the likelihood that a contaminant is a human carcinogen and the conditions under which the carcinogenic effects may be expressed (USEPA, 2005). A narrative is developed to provide a complete description of the weight of evidence evaluation and conditions of carcinogenicity. The potential carcinogenicity descriptors presented in the EPA's 2005 guidelines are:

- Carcinogenic to Humans
- Likely to Be Carcinogenic to Humans
- Suggestive Evidence of Carcinogenic Potential
- Inadequate Information to Assess Carcinogenic Potential
- Not Likely to Be Carcinogenic to Humans

More than one carcinogenicity descriptor can be applied in cases when a chemical's carcinogenic effects differ by dose, exposure route, or mode of action (MOA)[1]. MOA information informs both the qualitative and quantitative aspects of the assessment, including the human relevance of tumors observed in animals. The MOA analysis must be conducted separately for each target organ/tissue type according to EPA guidance (USEPA, 2005).

[1]MOA is defined as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. It is contrasted with "mechanism of action," which implies a more detailed understanding and description of events.

3 Cancer Weight of Evidence for Carcinogenicity and Cancer Classification

3.1 PFOA

3.1.1 Summary of the Weight of Evidence

The carcinogenicity of PFOA has been documented in both epidemiological and animal toxicological studies. The evidence from *medium* quality epidemiological studies is primarily based on the incidence of kidney and testicular cancer, as well as some evidence of increased breast cancer incidence in susceptible subpopulations. Other cancer types have been observed in humans, although the evidence for these is generally limited to *low* confidence studies. The evidence of carcinogenicity in animal models is provided in three *high* or *medium* confidence chronic oral animal bioassays in Sprague-Dawley rats which together identified neoplastic lesions of the liver, pancreas, and testes. The available mechanistic data suggest that multiple MOAs could play a role in the renal, testicular, pancreatic, and hepatic tumorigenesis associated with PFOA exposure in human populations as well as animal models.

The strongest evidence of an association between PFOA exposure and cancer in human populations is from studies of kidney cancer. Two *medium* confidence studies of the C8 Health Project population reported positive associations between PFOA levels (mean at enrollment 0.024 μg/mL) and kidney cancer among the residents living near the DuPont plant in Parkersburg, West Virginia (Barry et al., 2013; Vieira et al., 2013). Vieira et al. (2013) reported elevated risk of kidney cancer in residents of the Little Hocking water district of Ohio (OR: 1.7, 95% CI: 0.4, 3.3; n = 10) and the Tuppers Plains water district of Ohio (OR: 2.0, 95% CI: 1.3, 3.1; n = 23). Barry et al. (2013) extended this work, and found increased risk of kidney cancer (HR: 1.10, 95% CI: 0.98, 1.24; n = 105), though the levels did not reach statistical significance. The high-exposure occupational study by Steenland and Woskie (2012) evaluated kidney cancer mortality in workers from West Virginia and observed significant elevated risk of kidney cancer death in the highest exposure quartile. As part of the C8 Health Project, the C8 Science Panel (2012) concluded a probable link between PFOA exposure and kidney cancer (Steenland et al., 2020).

The findings of another recently published *medium* quality study add support to the previous evidence of an association between PFOA and kidney cancer (Shearer et al., 2021). Shearer et al. (2021) is a multi-center case-control study nested within the National Cancer Institute (NCI) Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial (n = 326). The authors reported a statistically significant increase in risk of renal cell carcinoma (RCC) with pre-diagnostic serum levels of PFOA (OR = 2.63; 95% CI: 1.33, 5.20 for the highest vs. lowest quartiles; p-trend = 0.007, or per doubling of PFOA: OR: 1.71; 95% CI: 1.23, 2.37). The association remained significant in analyses on a per doubling increase in PFOA after adjusting for other PFAS. The increase in the highest exposure quartile remained and the magnitude was similar (i.e., OR = 2.63 without adjusting for other PFAS vs. 2.19 after adjusting for other PFAS), but it was no longer statistically significant. Statistically significant increased odds of RCC were observed in a subgroup of participants ages 55–59 years, and in men and in women, analyzed separately. A recent critical review and meta-analysis of the epidemiological literature concluded that there was an increased risk for kidney tumors (16%) for every 10 ng/mL increase

in serum PFOA (Bartell and Vieira, 2021). Although the authors concluded that the associations were likely causal, they noted the limited number of studies and therefore, additional studies with larger cohorts would strengthen the conclusion. Taken together, the recent pooled analysis of the NCI nested case-control study (Shearer et al., 2021) of 324 cases and controls and the C8 Science Panel Study (Barry et al., 2013) of 103 cases and 511 controls provide evidence of concordance in kidney cancer findings from studies of the general population and studies of high-exposure communities (Steenland et al., 2022). CalEPA (2021) similarly concluded, "[t]here is evidence from epidemiologic studies that exposure to PFOA increases the risk of kidney cancer."

There is also evidence of associations between PFOA serum concentrations and testicular cancer in humans, though no new epidemiological studies reporting these associations have been published since the studies described in the EPA's 2016 PFOA HESD (USEPA, 2016b). Similar to their results for kidney cancer, Vieira et al. (2013) reported an increased adjusted OR for testicular cancer (OR: 5.1, 95% CI: 1.6, 15.6; n = 8) in residents of the Little Hocking water district of Ohio. Barry et al. (2013) also found significantly increased testicular cancer risk with an increase in estimated cumulative PFOA serum levels (HR: 1.34, 95% CI: 1.00, 1.79; n = 17). The C8 Science Panel (2012) concluded that a probable link also exists between PFOA exposure and testicular cancer (Steenland et al., 2020). A recent critical review and meta-analysis of the epidemiological literature concluded that there was an increased risk for testicular tumors (3%) for every 10 ng/mL increase in serum PFOA (Bartell and Vieira, 2021) (see Appendix A, Table A-42, USEPA (2024e)). In their review of the available epidemiological data, IARC (2016) concluded that the evidence for testicular cancer was "considered credible and unlikely to be explained by bias and confounding, however, the estimate was based on small numbers." Similarly, CalEPA (2021) concluded, "[o]verall, the epidemiologic literature to date suggests that PFOA is associated with testicular cancer."

The majority of epidemiological studies examining the carcinogenicity after PFOA exposure reported on breast cancer risk. Two nested case-control studies found associations between PFOA exposure and breast cancer, but only in participants with known genetic susceptibility (e.g., specific genotype or tumor estrogen receptor (ER) type) (Mancini et al., 2020; Ghisari et al., 2017). In Taiwan, Tsai et al. (2020) observed an increased risk of breast cancer only in all women 50 years old or younger (including ER+ and ER– participants), and in ER+ participants aged 50 years or younger, along with a decrease in risk for ER– breast cancers in participants aged 50 years or younger. Significantly increased odds of breast cancer were also observed in an NHANES population across serum PFOA quartiles with a significant dose-response trend (Omoike et al., 2021). Two nested case-control studies did not report an association between breast cancer and PFOA concentrations measured in maternal serum throughout pregnancy and 1–3 days after delivery (Cohn et al., 2020) or in serum after case diagnosis and breast cancer (Hurley et al., 2018). One nested case-cohort study did not report an association between breast cancer and PFOA concentrations measured in a group of predominantly premenopausal women (Bonefeld-Jørgensen et al., 2014). In the C8 Health Project cohort, Barry et al. (2013) observed a significant inverse association with breast cancer for both unlagged (i.e., concurrent) and 10-year lagged (i.e., cumulative exposures occurring 10 years in the past) estimated cumulative PFOA serum concentrations. Similarly, a recent study in a Japanese population reported an inverse association across serum PFOA quartiles with a significant dose-response trend (Itoh et al., 2021). Overall, study design differences, lack of replication of the results, and a lack of

mechanistic understanding of specific breast cancer subtypes or susceptibilities of specific populations limit firm conclusions regarding PFOA and breast cancer. However, there is suggestive evidence that PFOA exposure may be associated with an increased breast cancer risk based on studies in populations with specific genetic polymorphisms conferring increased susceptibility and for specific types of breast tumors.

In addition to the available epidemiological data, two multi-dose bioassays and one single-dose chronic cancer bioassay are available that investigate the relationship between dietary PFOA exposure and carcinogenicity in male and female rats (NTP, 2020b; Butenhoff et al., 2012b; Biegel et al., 2001). Increased incidences of neoplastic lesions were primarily observed in male rats, though results in females are supportive of potential carcinogenicity of PFOA. Testicular Leydig cell tumors (LCTs) were identified in both the Butenhoff et al. (2012b) and Biegel et al. (2001) studies. LCT incidence at similar dose levels was comparable between the two studies (11% and 14%). Pancreatic acinar cell tumors (PACTs) were observed in both the NTP (2020b) and Biegel et al. (2001) studies. NTP (2020b) reported increased incidences of pancreatic acinar cell adenomas and adenocarcinomas in males in all treatment groups compared to their respective controls. These pancreatic tumor types were also observed in female rats in the highest dose group, a rare occurrence compared to historical controls (0/340), though these increases did not reach statistical significance. Biegel et al. (2001) similarly reported increases in the incidence of PACTs in male rats treated with PFOA, with zero incidences observed in control animals. In addition, NTP (2020b) reported dose-dependent increases in the incidence of liver adenomas and carcinomas in male rats and Biegel et al. (2001) also observed increased incidence of adenomas in male rats. Overall, NTP concluded that in their 2-year feeding studies, there was *clear evidence* of carcinogenic activity of PFOA in male Sprague-Dawley rats and *some evidence* of carcinogenic activity of PFOA in female Sprague-Dawley rats based on the observed tumor types (NTP, 2020b).

The report from NTP (2020b) provides evidence that chronic oral exposure accompanied by perinatal exposure (i.e., exposure beginning at gestation day 5 through lactation) to PFOA does not increase cancer risk when compared to chronic exposure scenarios beginning during the postnatal (i.e., exposure initiated after weaning) stage. The incidences of all tumor types examined did not differ significantly between the treatment groups administered PFOA during both perinatal and postweaning periods compared with the postweaning-only treatment groups (see further study design details in Section 3.4.4.2.1.2 of the *Final Human Health Toxicity Assessment for PFOA* (USEPA, 2024e). Lifestage-dependent sensitivity to the carcinogenic effects of PFOA exposure was previously assessed in the study by Filgo et al. (2015) which exposed two mouse strains during gestation only (i.e., prenatal exposure with no comparisons to mice exposed through adulthood). Filgo et al. (2015) observed a non-monotonic increase in hepatocellular adenomas in the female offspring of one strain (CD-1) and hepatocellular adenoma incidence in approximately 13% of all PFOA-exposed peroxisome proliferator-activated receptor (PPAR) α-knockout mice. However, these results are not conclusive due to the study's limited sample size and study design.

In the 2016 PFOA HESD (USEPA, 2016b), the EPA concluded that the induction of tumors was likely due to multiple MOAs, specifically noting interactions with nuclear receptors, perturbations in the endocrine system, interruption of intercellular communication, mitochondrial effects, and/or perturbations in the DNA replication and cell division processes. Since that time,

the available mechanistic data continue to suggest that multiple MOAs could play role in the renal, testicular, pancreatic, and hepatic tumorigenesis associated with PFOA exposure in human populations as well as animal models. The few available mechanistic studies focusing on PFOA-induced renal toxicity highlight several potential underlying mechanisms of PFOA exposure-induced renal tumorigenesis, including altered cell proliferation and apoptosis, epigenetic alterations, and oxidative stress. However, due to data limitations, it is difficult to distinguish which mechanism(s) are operative for PFOA-induced kidney cancer. Similarly for testicular cancer, the available literature highlights several potential MOAs by which PFOA exposure may result in increased incidence of LCTs in animals, though it is unclear whether these MOAs are relevant to testicular cancers associated with PFOA exposure in humans. Combined, the epidemiological and animal toxicological literature indicate that the testes are a common site of PFOA-induced tumorigenesis. A full MOA analysis, including in-depth discussions on the potential MOAs for kidney and testicular tumors, as well as discussions on the potential MOAs and human relevance for pancreatic and liver tumors observed in rats, is presented in Section 3.5.4.2 of the *Final Human Health Toxicity Assessment for PFOA* (USEPA, 2024e). Overall, the EPA concluded that the available mechanistic data suggest that multiple MOAs could play role in the renal, testicular, pancreatic, and hepatic tumorigenesis associated with PFOA exposure in studies of human populations and animal models. IARC (Zahm et al., 2023; IARC, 2016), CalEPA (CalEPA, 2021) and NJDWQI (Gleason et al., 2017) similarly concluded that there is evidence for many potential mechanisms for PFOA-induced carcinogenicity. For example, IARC concluded there is strong mechanistic evidence of carcinogenicity in exposed humans and that PFOA is immunosuppressive, induces epigenetic alterations, induces oxidative stress, modulates receptor-mediated effects (via (PPAR) α, constitutive androstane receptor/pregnane X receptor [CAR/PXR], and PPARγ), and alters cell proliferation, cell death, and nutrient and energy supply (Zahm et al., 2023).

3.1.2 Cancer Classification

3.1.2.1 PFOA Is Determined to be Likely to Be Carcinogenic to Humans

Under the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005), the EPA reviewed the weight of the evidence and determined that PFOA is *Likely to Be Carcinogenic to Humans*, as "the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor *Carcinogenic to Humans.*" This determination is based on the evidence of kidney and testicular cancer in humans and LCTs, PACTs, and hepatocellular adenomas in rats.

The *Guidelines* (USEPA, 2005) provide examples of data that may support the *Likely to Be Carcinogenic to Humans* descriptor; the available PFOA data are consistent with the following factors:

- "an agent demonstrating a plausible (but not definitively causal) association between human exposure and cancer, in most cases with some supporting biological, experimental evidence, though not necessarily carcinogenicity data from animal experiments";
- "an agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans";

- "a rare animal tumor response in a single experiment that is assumed to be relevant to humans";
- "a positive tumor study that is strengthened by other lines of evidence, for example, either plausible (but not definitively causal) association between human exposure and cancer or evidence that the agent or an important metabolite causes events generally known to be associated with tumor formation (such as DNA reactivity or effects on cell growth control) likely to be related to the tumor response in this case" (USEPA, 2005).

The available evidence indicates that PFOA has carcinogenic potential in humans and at least one animal model. A plausible, though not definitively causal, association exists between human exposure to PFOA and kidney and testicular cancers in the general population and highly exposed populations. As stated in the *Guidelines for Carcinogen Risk Assessment,* "an inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies." Two *medium* confidence independent studies provide evidence of an association between kidney cancer and elevated PFOA serum concentrations (Shearer et al., 2021; Vieira et al., 2013), while two studies in the same cohort provide evidence of an association between testicular cancer and elevated PFOA serum concentrations (Barry et al., 2013; Vieira et al., 2013). The PFOA cancer database would benefit from additional large *high* confidence cohort studies in independent populations.

The evidence of carcinogenicity in animals is based on three studies that used the same strain of rat. Taken together, these results provide evidence of increased incidence of three different tumor types (LCTs, PACTs, and hepatocellular tumors) in males administered diets contaminated with PFOA. Additionally, pancreatic acinar cell adenocarcinomas are a rare tumor type (NTP, 2020b), and their occurrence in PFOA-treated animals in this study increases the confidence that this incidence is treatment-related since these tumors are unlikely to be observed in the absence of a carcinogenic agent (USEPA, 2005). The historical control incidence for pancreatic acinar cell adenocarcinomas in the female rats is 0/340 and in the male rats is 2/340, highlighting the rarity of this particular tumor type (NTP, 2020b). Importantly, site concordance is not always assumed between humans and animal models; agents observed to produce tumors may do so at the same or different sites in humans and animals (USEPA, 2005). While site concordance was present between human studies of testicular cancer and animal studies reporting increased incidence of LCTs, evidence of carcinogenicity of PFOA from other cancer sites where concordance between humans and animals is not present is still relevant to the carcinogenicity determination for PFOA. See Table A below for specific rationale on how PFOA aligns with examples supporting the *Likely to Be Carcinogenic to Humans* cancer descriptor in the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005).

Table A. Comparison of the PFOA Carcinogenicity Database with the *Likely* Cancer Descriptor as Outlined in the Guidelines for Carcinogen Risk Assessment (USEPA, 2005)

Likely to Be Carcinogenic to Humans	
"An agent demonstrating a plausible (but not definitively causal) association between human exposure and cancer, in most cases with some supporting biological, experimental evidence, though not necessarily carcinogenicity data from animal experiments." (USEPA, 2005)	**PFOA data are consistent with this description.** Epidemiological evidence supports a plausible association between PFOA exposure and kidney and testicular cancer, though there are uncertainties regarding the MOAs for tumor types observed in humans. There is supporting experimental evidence, including carcinogenicity data from animal experiments.
"An agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans." (USEPA, 2005)	**PFOA data are consistent with this description.** PFOA has tested positive in one species (rat), both sexes, and multiple sites (liver, pancreas, testes, uterus). There is also evidence of carcinogenicity in humans.
"A positive tumor study that raises additional biological concerns beyond that of a statistically significant result, for example, a high degree of malignancy, or an early age at onset." (USEPA, 2005)	**This description is not applicable to PFOA.** The report by NTP (2020b) does not indicate that perinatal exposure exacerbates the carcinogenic potential of PFOA.
"A rare animal tumor response in a single experiment that is assumed to be relevant to humans." (USEPA, 2005)	**PFOA data are consistent with this description.** The pancreatic adenocarcinomas observed in multiple male dose groups are a rare tumor type in this strain (NTP, 2020b).
"A positive tumor study that is strengthened by other lines of evidence, for example, either plausible (but not definitively causal) association between human exposure and cancer or evidence that the agent or an important metabolite causes events generally known to be associated with tumor formation (such as DNA reactivity or effects on cell growth control) likely to be related to the tumor response in this case." (USEPA, 2005)	**PFOA data are consistent with this description.** Multiple positive tumor studies in the same strain of rat are supported by plausible associations between human exposure and kidney and testicular cancer.

Notes: DNA = deoxyribonucleic acid; MOA = mode of action.

The EPA recognizes that other state and international health agencies have recently classified PFOA as carcinogenic to humans (IARC as reported in Zahm et al., 2023; CalEPA, 2021). As the SAB PFAS Panel (USEPA, 2022c) noted, "the criteria used by California EPA, for determination that a chemical is a carcinogen, are not identical to the criteria in the U.S. EPA's *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005)" and, similarly, IARC's classification criteria are not identical to the EPA's guidelines (IARC, 2019). Rationale for why PFOA does not meet the *Carcinogenic to Humans* descriptor according to the EPA's *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005) is detailed in the following section.

3.1.2.2 PFOA Surpasses the Suggestive but Does Not Meet the Carcinogenic to Humans Classification

While reviewing the weight of evidence for PFOA, the EPA also evaluated consistencies of the carcinogenicity database with other cancer descriptors according to the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005). In the 2016 PFOA HESD, the EPA determined that the available carcinogenicity database for PFOA at that time was consistent with the descriptions for *Suggestive Evidence of Carcinogenic Potential* (USEPA, 2016b). Upon reevaluation for this assessment, the agency identified several new studies reporting on cancer

outcomes that strengthened the evidence. As a result of conducting a weight of evidence evaluation of the available carcinogenicity database, the EPA determined that PFOA is consistent with the descriptions for *Likely to Be Carcinogenic to Humans* according to the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005), as described above. More specifically, the available data for PFOA surpass many of the descriptions for *Suggestive Evidence of Carcinogenic Potential* provided in the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005). The examples for which the PFOA database exceeds the *Suggestive* descriptions (outlined below) include:

- "a small, and possibly not statistically significant, increase in tumor incidence observed in a single animal or human study that does not reach the weight of evidence for the descriptor "Likely to Be Carcinogenic to Humans." The study generally would not be contradicted by other studies of equal quality in the same population group or experimental system (see discussions of conflicting evidence and differing results, below);
- a small increase in a tumor with a high background rate in that sex and strain, when there is some but insufficient evidence that the observed tumors may be due to intrinsic factors that cause background tumors and not due to the agent being assessed;
- a statistically significant increase at one dose only, but no significant response at the other doses and no overall trend" (USEPA, 2005).

There are multiple *medium* or *high* confidence human and animal toxicological studies that provide evidence of multiple tumor types resulting from exposure to PFOA. The observed tumor types are generally consistent across human subpopulations (i.e., kidney (Shearer et al., 2021; Vieira et al., 2013) and testicular (Barry et al., 2013; Vieira et al., 2013)) and studies of equal quality did not provide conflicting evidence for these cancer types. Studies within the same species of rat are consistently demonstrating multi-site tumorigenesis (i.e., testicular, pancreatic, and hepatic (NTP, 2020b; Butenhoff et al., 2012b; Biegel et al., 2001)) and there is no indication that a high background incidence or other intrinsic factors related to these tumor types are driving the observed responses. The SAB PFAS Review Panel agreed that: "a) the evidence for potential carcinogenicity of PFOA has been strengthened since the 2016 HESD; b) the results of human and animal studies of PFOA are consistent with the examples provided above and support a designation of 'likely to be carcinogenic to humans'; and c) the data exceed the descriptors for the three designations lower than 'likely to be carcinogenic'" (USEPA, 2022b). See Table B below for specific details on how PFOA exceeds the examples supporting the *Suggestive Evidence of Carcinogenic Potential* cancer descriptor in the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005).

While the SAB panel agreed that the data for PFOA exceed a *Suggestive* cancer descriptor, the final report also recommends "explicit description of how the available data for PFOA do not meet the criteria for the higher designation as "carcinogenic" (USEPA, 2022b). After reviewing the descriptions of the descriptor *Carcinogenic to Humans,* the EPA has determined that at this time, the evidence supporting the carcinogenicity of PFOA does not warrant a descriptor exceeding *Likely to Be Carcinogenic to Humans*. The *Guidelines* indicate that a chemical agent can be deemed *Carcinogenic to Humans* if it meets all of the following conditions:

- "there is strong evidence of an association between human exposure and either cancer or the key precursor events of the agent's mode of action but not enough for a causal association, and
- there is extensive evidence of carcinogenicity in animals, and
- the mode(s) of carcinogenic action and associated key precursor events have been identified in animals, and
- there is strong evidence that the key precursor events that precede the cancer response in animals are anticipated to occur in humans and progress to tumors, based on available biological information" (USEPA, 2005).

As discussed in the subsection above, convincing epidemiological evidence supporting a causal association between human exposure to PFOA and cancer are currently lacking. The SAB similarly concluded that "the available epidemiologic data do not provide convincing evidence of a causal association but rather provide evidence of a plausible association, and thus do not support a higher designation of 'carcinogenic to humans'" (USEPA, 2022b).

Additionally, though the available evidence indicates that there are positive associations between PFOA and multiple cancer types, there is uncertainty regarding the identification of carcinogenic MOA(s) for PFOA, particularly for renal cell carcinomas and testicular cancer in humans. The evidence of carcinogenicity in animals is limited to a single strain of rat, although PFOA tested positive for multi-site tumorigenesis. The animal database does not provide clarity to discern the MOA(s) of PFOA in humans, though there is some animal toxicological study evidence supporting hormone-mediated MOAs for testicular tumors and oxidative stress-mediated MOAs for pancreatic tumors. The full mode of action analysis, including in-depth discussions on the potential MOAs for kidney and testicular tumors, as well as discussions on the potential MOAs and human relevance for pancreatic and liver tumors observed in rats, is presented in Section 3.5.4.2 of the *Final Human Health Toxicity Assessment for PFOA*(USEPA, 2024e). See Table B below for specific details on how PFOA does not align with the examples supporting the *Carcinogenic to Humans* cancer descriptor in the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005).

Table B. Comparison of the PFOA Carcinogenicity Database with Cancer Descriptors as Outlined in the Guidelines for Carcinogen Risk Assessment (USEPA, 2005)

Comparison of Evidence for *Suggestive* and *Carcinogenic* Cancer Descriptors	
Suggestive Evidence of Carcinogenic Potential	
"A small, and possibly not statistically significant, increase in tumor incidence observed in a single animal or human study that does not reach the weight of evidence for the descriptor "Likely to Be Carcinogenic to Humans." The study generally would not be contradicted by other studies of equal quality in the same population group or experimental system." (USEPA, 2005)	**PFOA data exceed this description.** Statistically significant increases in tumor incidence of multiple tumor types were observed across several human and animal toxicological studies.
"A small increase in a tumor with a high background rate in that sex and strain, when there is some but insufficient evidence that the observed tumors may be due to intrinsic factors that cause background	**This description is not applicable to the tumor types observed after PFOA exposure.**

Comparison of Evidence for *Suggestive* and *Carcinogenic* Cancer Descriptors	
tumors and not due to the agent being assessed." (USEPA, 2005)	
"Evidence of a positive response in a study whose power, design, or conduct limits the ability to draw a confident conclusion (but does not make the study fatally flawed), but where the carcinogenic potential is strengthened by other lines of evidence (such as structure-activity relationships)." (USEPA, 2005)	**PFOA data exceed this description.** The studies from which carcinogenicity data are available were determined to be *high* or *medium* confidence during study quality evaluation.
"A statistically significant increase at one dose only, but no significant response at the other doses and no overall trend." (USEPA, 2005)	**PFOA data exceed this description.** Increases in kidney cancer in humans were statistically significant in two exposure groups in one study (Vieira et al., 2013) and there was a statistically significant increasing trend across exposure quartiles in a second study (Shearer et al., 2021). Increases in hepatic and pancreatic tumors in male rats were observed in multiple dose groups with a statistically significant trend overall (NTP, 2020b).
Carcinogenic to Humans	
"This descriptor is appropriate when there is convincing epidemiologic evidence of a causal association between human exposure and cancer." (USEPA, 2005)	**PFOA data are not consistent with this description.** There is evidence of a plausible association between PFOA exposure and cancer in humans, however, the database is limited to only two independent populations, there is uncertainty regarding the potential confounding of other PFAS, and there is limited mechanistic information that could contribute to the determination of a causal relationship.
Or, this descriptor may be equally appropriate with a lesser weight of epidemiologic evidence that is strengthened by other lines of evidence. It can be used when *all* of the following conditions are met:	
"There is strong evidence of an association between human exposure and either cancer or the key precursor events of the agent's MOA but not enough for a causal association." (USEPA, 2005)	**PFOA data are not consistent with this description.** There is evidence of an association between human exposure and cancer, however, there is limited mechanistic information that could contribute to the determination of a causal relationship.
"There is extensive evidence of carcinogenicity in animals." (USEPA, 2005)	**PFOA data are not consistent with this description.** While there are three chronic cancer bioassays available, each testing positive in at least one tumor type, they were all conducted in the same strain of rat. The database would benefit from *high* confidence chronic studies in other species and/or strains.
"The mode(s) of carcinogenic action and associated key precursor events have been identified in animals." (USEPA, 2005)	**PFOA data are not consistent with this description.** A definitive MOA has not been identified for each of the PFOA-induced tumor types identified in rats.
"There is strong evidence that the key precursor events that precede the cancer response in animals are anticipated to occur in humans and progress to tumors, based on available biological information." (USEPA, 2005)	**PFOA data are not consistent with this description.** The animal database does not provide significant clarity on the MOA(s) of PFOA in humans, though there is some evidence supporting hormone-mediated MOAs for testicular tumors and oxidative stress-mediated MOAs for pancreatic tumors.

Notes: MOA = mode of action.

3.2 PFOS

3.2.1 Summary of the Weight of Evidence

The carcinogenicity of PFOS has been documented in both epidemiological and animal toxicological studies. The available epidemiology studies report elevated risk of liver, bladder, kidney, prostate, and breast cancers after chronic PFOS exposure in some studies, though limited evidence for some tumor types (i.e., liver and renal) and mixed results for other tumor types (i.e., bladder, prostate, breast) provide plausible but not definitively causal evidence of a relationship between PFOS exposure and cancer outcomes from the epidemiological evidence alone. The animal chronic cancer bioassay provides additional support for carcinogenicity with the identification of multi-site tumorigenesis (liver and pancreas) in both male and female rats. The available mechanistic data suggest that multiple MOAs could play role in the hepatic and pancreatic tumorigenesis associated with PFOS exposure based on animal model study findings.

Results for liver cancer from occupational (Alexander et al., 2003) and general population-based (Eriksen et al., 2009) studies of PFOS exposure published ~15–20 years ago were generally imprecise (i.e., null results with wide confidence intervals), but more recent studies have reported statistically significant increased risk of liver cancer associated with increased PFOS exposure (Cao et al., 2022; Goodrich et al., 2022). A nested case-control study of adults from the Multiethnic Cohort study reported a significant increased risk of liver cancer when comparing those in the 85th percentile of PFOS exposure to those at or below the 85th percentile (Goodrich et al., 2022). Positive, but not statistically significant, associations were observed in analyses of continuous PFOS exposure which supported the study's overall conclusion of an increased risk of liver cancer with increasing PFOS exposure. The study's sensitivity was limited by the small number of cases and controls (n = 50 each). Consistent with this finding, a Chinese general population case-control study of children and adults reported a significant increase in risk of liver cancer in analyses of continuous PFOS exposure; however, the study was considered *low* confidence due to lack of information on control selection, outcome ascertainment, and statistical analysis (Cao et al., 2022).

Studies of the association between PFOS serum concentrations and bladder cancer have mixed (positive and null) findings. An elevated risk of bladder cancer mortality was associated with PFOS exposure in an occupational study (Alexander et al., 2003) but a subsequent study to ascertain cancer incidence in this cohort with four additional years of observation observed elevated but not statistically significant incidence ratios that were 1.7- to 2-fold higher among workers with higher cumulative exposure to PFOS (Alexander and Olsen, 2007). Some of the limitations of these studies include the lack of precision of the risk estimates due to the small number of cases, and the lack of control for the potential confounding of smoking. A nested case-control study in a general population Danish cohort did not observe elevated bladder cancer risk with increasing PFOS serum levels (Eriksen et al., 2009). Overall, there is suggestive evidence of a relationship between PFOS exposure and bladder cancer, particularly for high-exposure communities.

One study in the general population reported a statistically significant increase in risk of RCC in the highest PFOS exposure quartile and in continuous analyses of PFOS exposure (i.e., per doubling of PFOS concentration) (Shearer et al., 2021). Although the trend was significant across quartiles, the effect in the third quartile was null. Additionally, the association with PFOS

was attenuated after adjusting for other PFAS, and it was lower in the third quartile than in the second quartile, indicating potential confounding by correlated PFAS exposures. There was no reported association when evaluated on a per doubling of PFOS after adjusting for other PFAS.

Elevated non-significant ORs for prostate cancer were reported for the occupationally exposed cohort examined by Alexander and Olsen (2007) and the Danish population-based cohort examined by Eriksen et al. (2009). In the same occupational cohort studied by Alexander and Olsen (2007), Grice et al. (2007) observed that prostate cancers were among the most frequently reported cancers. When cumulative PFOS exposure measures were analyzed, elevated ORs were reported for prostate cancer, however, they did not reach statistical significance. Length of follow-up may not have been adequate to detect cancer incidence in this cohort as approximately one-third of the participants had worked < 5 years in their jobs, and only 41.7% were employed ≥ 20 years (Grice et al., 2007). No association between PFOS exposure and prostate cancer was reported in either a second case-control study in Denmark (Hardell et al., 2014) or in a study of the association between PFOS serum concentrations and prostate specific antigen (a biomarker of prostate cancer) from the C8 Health Project (Ducatman et al., 2015). In an NHANES population, Omoike et al. (2021) observed a significantly inverse association between PFOS exposure and prostate cancer.

The majority of studies examining associations between PFOS exposure and cancer outcomes were on breast cancer. One study of Inuit females in Greenland observed positive associations between PFOS levels and risk for breast cancer (Bonefeld-Jorgensen et al., 2011), although the association was of a low magnitude and could not be separated from the effects of other perfluorosulfonated compound exposures (i.e., perfluorohexanesulfonate and perfluorooctanesulfonamide). Three studies indicated potential associations between PFOS exposure and increased breast cancer risk in specific subgroups or increased risk for specific breast cancer subtypes. Ghisari et al. (2017) reported that increased breast cancer risk was associated with increased PFOS serum concentrations in Danish individuals with a specific polymorphism in the cytochrome P450 aromatase gene (for aromatase, associated with estrogen biosynthesis and metabolism). Mancini et al. (2020) reported that increased PFOS serum concentrations were associated specifically with increased risk of ER+ and PR+ tumors, whereas risk of ER– and PR– tumors did not follow a dose-dependent response. In a Taiwanese population, Tsai et al. (2020) observed a statistically significant increased risk of breast cancer in all women 50 years old or younger (including ER+ and ER– participants), and in ER+ participants aged 50 years or younger. Statistically significant increases in breast cancer risk were also observed in an NHANES population in the two highest quartiles of exposure, but the association was inverse in the second quartile (Omoike et al., 2021). No association was identified between PFOS and breast cancer in either case-control or nested case-control studies of Danish and California cancer registry populations, respectively (Hurley et al., 2018; Bonefeld-Jørgensen et al., 2014). Another general population study in the U.S. suggested that maternal PFOS exposure combined with high maternal cholesterol may decrease the daughters' risk of breast cancer but did not examine breast cancer subtypes or individuals with genetic variants that may have increased susceptibility (Cohn et al., 2020). A recent study in a Japanese population observed an inverse association across serum PFOS quartiles with a significant dose-response trend (Itoh et al., 2021). The association remained significantly inverse in both pre- and postmenopausal women in the highest tertile of exposure, with a significant dose-response trend. However, in some of the studies PFOS levels were measured after or near the time of cancer

diagnosis (Omoike et al., 2021; Tsai et al., 2020). Given the long half-life of PFOS in human blood, the exposure levels measured in these studies could represent exposures that occurred prior to cancer development. However, this is currently difficult to evaluate since data on the latency of PFOS exposure and subsequent cancer assessment is not available. Overall, study design limitations with specific studies, lack of replication of the results, and a lack of mechanistic understanding of specific breast cancer subtypes or susceptibilities of specific populations limit firm conclusions regarding PFOS and breast cancer. However, there is suggestive evidence that PFOS exposure may be associated with an increased breast cancer risk based on studies in susceptible populations, such as those with specific polymorphisms and for specific types of breast tumors.

One available chronic toxicity/carcinogenicity bioassay for PFOS, a 104-week dietary study in rats, provides evidence of multi-sex and multi-site tumorigenesis resulting from PFOS exposure (Butenhoff et al., 2012a; Thomford, 2002). This study was originally published as a 3M-sponsored report by Thomford (2002) and some of the data were later published in a peer-reviewed article by Butenhoff et al. (2012a). Statistically significant increases in the incidence of hepatocellular adenomas in the high-dose (20 ppm) male (7/43; 16%) and female rat groups (5/31; 16%) and combined adenomas/carcinomas in the females (6/32; 19%; five adenomas, one carcinoma) were observed. The observation of one carcinoma in the female rats is a relatively rare occurrence according to NTP's historical controls for female Sprague-Dawley rats (1/639 historical control incidence) (NTP, 2020a). Historical control incidence rates for these tumor types were not provided by Thomford (2002). Additionally, there were statistically significant dose-related trends in the hepatic tumor responses of both males and females. A statistically significant trend of increased incidence of pancreatic islet cell carcinomas with increased PFOS dose was also observed in the male rats, though the individual dose groups were not statistically different from the control group. The percentages of animals with islet cell carcinomas in the highest dose group (12.5%) exceeds NTP's historical controls for male Sprague-Dawley rats by over an order of magnitude (12/638; 1.9%) (NTP, 2020a).

Thyroid tumors (follicular cell adenomas and carcinomas) were observed in males and females, though these responses were not statistically significant in any dose group, nor was there a linear dose-response trend (Butenhoff et al., 2012a; Thomford, 2002). In males, the incidence of thyroid tumors was significantly elevated only in the high-dose, recovery group males exposed for 52 weeks (10/39) but not in the animals receiving the same dose for 105 weeks. However, Thomford (2002) indicated that the number of thyroid tumors observed in the recovery group males were outside the range of historical control values at that time, similar to what NTP (2020a) has reported for its laboratories (3/637 combined follicular cell adenoma or carcinoma). There were few follicular cell adenomas/carcinomas in the females (4 total, excluding the recovery group) with a nonlinear dose response. Mammary gland tumors, primarily combined fibroma adenoma and adenoma, were also observed in females, though there was a high background incidence of mammary gland tumors in the control animals, and the incidence lacked dose response for all tumor classifications.

Based on the weight of evidence evaluation of the available peer-reviewed scientific evidence, PFOS has the potential to induce hepatic tumors in humans and rodents via multiple MOAs, most notably via the modulation of nuclear receptors (i.e., PPARα and CAR) and cytotoxicity. There is also limited evidence supporting additional potential MOAs of genotoxicity,

immunosuppression, and oxidative stress. The conclusions from the weight of evidence analysis of the available data for PFOS are consistent with literature reviews recently published by two state health agencies which concluded that the hepatotoxic effects of PFOS are not entirely dependent on PPARα activation (CalEPA, 2021; NJDWQI, 2018). Similarly, IARC (Zahm et al., 2023) found strong mechanistic evidence of carcinogenicity in exposed humans and that PFOS is immunosuppressive and induces epigenetic alterations in humans, induces oxidative stress in human primary cells and experimental systems and modulates multiple receptors. No established MOA was identified for pancreatic islet cell carcinogenicity in animals. A full mode of action analysis, including in-depth discussions on the potential MOAs for hepatic and pancreatic tumors is presented in Section 3.5.4 of the *Final Human Health Toxicity Assessment for PFOS* (USEPA, 2024d). Overall, the EPA concluded that there is an absence of definitive mechanistic data supporting a single MOA for PFOS and therefore, both tumor types may be relevant to humans in accordance with the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005).

3.2.2 Cancer Classification

3.2.2.1 PFOS Is Likely to Be Carcinogenic to Humans

Under the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005), the EPA reviewed the weight of the evidence and determined that PFOS is *Likely to Be Carcinogenic to Humans*, as "the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor *Carcinogenic to Humans.*" The *Guidelines* provide descriptions of data that may support the *Likely to Be Carcinogenic to Humans* descriptor; the available PFOS data are consistent with the following factors:

- "an agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans;
- a rare animal tumor response in a single experiment that is assumed to be relevant to humans; or
- a positive tumor study that is strengthened by other lines of evidence, for example, either plausible (but not definitively causal) association between human exposure and cancer or evidence that the agent or an important metabolite causes events generally known to be associated with tumor formation (such as DNA reactivity or effects on cell growth control) likely to be related to the tumor response in this case" (USEPA, 2005).

The available evidence indicates that PFOS has carcinogenic potential in one animal model for multiple sites and both sexes, as well as supporting evidence from human studies, consistent with the examples described in the *Guidelines for Carcinogen Risk Assessment* for the *Likely* descriptor. The epidemiological evidence of associations between PFOS and cancer found mixed results across tumor types. However, the available study findings support a plausible correlation between PFOS exposure and carcinogenicity in humans. The single chronic cancer bioassay performed in rats is positive for multi-site and -sex tumorigenesis (Butenhoff et al., 2012a; Thomford, 2002). In this study, statistically significant increases in the incidences of hepatocellular adenomas or combined adenomas and carcinomas were observed in both male and female rats. There was also a statistically significant trend of this response in both sexes indicating a relationship between the magnitude/direction of response and PFOS dose. As described in Section 3.5.4.2 of the *Final Human Health Toxicity Assessment for PFOS* (USEPA, 2024d), the available mechanistic evidence is consistent with multiple potential MOAs for this

tumor type; therefore, the hepatocellular tumors observed by Butenhoff et al./Thomford (2012a; 2002) may be relevant to humans. These findings in rats and their potential human relevance are supported by recent epidemiological studies that have reported associations between PFOS and hepatocellular carcinoma in humans (Cao et al., 2022; Goodrich et al., 2022).

In addition to hepatocellular tumors, Thomford (2002) reported increased incidences of pancreatic islet cell carcinomas with a statistically significant dose-dependent positive trend, as well as modest increases in the incidence of thyroid follicular cell tumors. The findings of multiple tumor types provide additional support for potential multi-site tumorigenesis resulting from PFOS exposure. Importantly, site concordance is not always assumed between humans and animal models; agents observed to produce tumors may do so at the same or different sites in humans and animals (USEPA, 2005). While site concordance was present between human studies of liver cancer and animal studies reporting increased incidence of hepatocellular tumors, evidence of carcinogenicity of PFOS from other cancer sites where concordance between humans and animals is not present is still relevant to the carcinogenicity determination for PFOS. See Table C below for specific details on how PFOS aligns with the examples supporting the *Likely to Be Carcinogenic to Humans* cancer descriptor in the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005).

Table C. Comparison of the PFOS Carcinogenicity Database with the *Likely* Cancer Descriptor as Outlined in the Guidelines for Carcinogen Risk Assessment (USEPA, 2005)

Likely to Be Carcinogenic to Humans	
"An agent demonstrating a plausible (but not definitively causal) association between human exposure and cancer, in most cases with some supporting biological, experimental evidence, though not necessarily carcinogenicity data from animal experiments." (USEPA, 2005)	**PFOS data are consistent with this description**. Epidemiological evidence supports a plausible association between PFOS exposure and liver cancer which is consistent with evidence of liver cancer in animals. Epidemiological studies evaluating the association between human exposure to PFOS and other cancers are mixed. Supporting carcinogenicity data are available from animal experiments.
"An agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans." (USEPA, 2005)	**PFOS data are consistent with this description**. PFOS has tested positive in animal experiments in more than one sex and site. Hepatic tumors were observed in male and female rats (statistically significant at high dose and statistically significant trend tests for each) and islet cell carcinomas show a statistically significant positive trend in male rats.
"A positive tumor study that raises additional biological concerns beyond that of a statistically significant result, for example, a high degree of malignancy, or an early age at onset." (USEPA, 2005)	**This description is not applicable to PFOS.**
"A rare animal tumor response in a single experiment that is assumed to be relevant to humans." (USEPA, 2005)	**PFOS data are consistent with this description**. The hepatocellular carcinoma observed in the high-dose female rats is a rare tumor type in this strain (NTP, 2020b).
"A positive tumor study that is strengthened by other lines of evidence, for example, either plausible (but not definitively causal) association between human exposure and cancer or evidence that the agent or an important metabolite causes events generally known to be	**PFOS data are consistent with this description.** The positive multi-site, multi-sex chronic cancer bioassay is supported by mechanistic data indicating that PFOS is associated with events generally known to be associated with tumor formation such as inducing nuclear receptor

Likely to Be Carcinogenic to Humans	
associated with tumor formation (such as DNA reactivity or effects on cell growth control) likely to be related to the tumor response in this case." (USEPA, 2005)	activation, cytotoxicity, genotoxicity, oxidative stress, and immunosuppression.

Notes: MOA = mode of action.

The EPA recognizes that other state and international health agencies have recently classified PFOS as either "possibly carcinogenic to humans" (IARC as reported in Zahm et al., 2023) or carcinogenic to humans (CalEPA, 2021). As the SAB PFAS Review Panel (USEPA, 2022c) noted, "the criteria used by California EPA, for determination that a chemical is a carcinogen, are not identical to the criteria in the U.S. EPA's *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005)" and, similarly, IARC's classification criteria are not identical to the EPA's guidelines (IARC, 2019). Rationale for why PFOS exceeds the *Suggestive Evidence of Carcinogenic Potential* descriptor and does not meet the *Carcinogenic to Humans* descriptor according to the EPA's *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005) is detailed in the following section.

3.2.2.2 PFOS Surpasses the Suggestive but Does Not Meet the Carcinogenic to Humans Classification

To provide further support for that PFOS is *Likely to Be Carcinogenic to Humans*, the EPA also evaluated consistencies of the carcinogenicity database with other cancer descriptors according to the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005). Upon reassessment of the PFOS carcinogenicity database, including the epidemiological, animal toxicological, and mechanistic databases, the agency has determined the available data for PFOS surpass many of the descriptions for *Suggestive Evidence of Carcinogenic Potential* according to the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005). The examples for which the PFOS database exceeds the *Suggestive Evidence* descriptions outlined in the *Guidelines for Carcinogen Risk Assessment* include:

- "a small, and possibly not statistically significant, increase in tumor incidence observed in a single animal or human study that does not reach the weight of evidence for the descriptor *Likely to Be Carcinogenic to Humans*;
- a small increase in a tumor with a high background rate in that sex and strain, when there is some but insufficient evidence that the observed tumors may be due to intrinsic factors that cause background tumors and not due to the agent being assessed;
- evidence of a positive response in a study whose power, design, or conduct limits the ability to draw a confident conclusion; and
- a statistically significant increase at one dose only, but no significant response at the other doses and no overall trend" (USEPA, 2005).

The strongest evidence for the carcinogenicity of PFOS is from one chronic animal bioassay which presents findings surpassing several of these criteria (Butenhoff et al., 2012a; Thomford, 2002). The Thomford/Butenhoff et al. (2012a; 2002) study is a *high* confidence study that observed statistically significant increases at individual dose levels and/or statistically significant trends in two tumor types and in one or more sexes, even with the relatively low dose levels used. The background incidence of these tumor types was low or negligible.

In the initial draft of this toxicity assessment (e.g., the *Proposed Approaches* document) (USEPA, 2021a) published for SAB review and the 2016 HESD (USEPA, 2016a), the EPA relied upon the tumor incidences provided in Butenhoff et al. (2012a), which is the peer-reviewed manuscript of an unpublished industry report – Thomford (2002). Upon further review of the results presented in the Thomford (2002) report prior to rule proposal (USEPA, 2023), the agency identified two factors that limited previous qualitative and quantitative interpretations of the data: 1) the Butenhoff et al. (2012a) study reported combined incidences of neoplastic lesions in the control and high-dose groups from the interim time point (52 weeks of dietary exposure; n = 10) and terminal time point (104 weeks of dietary exposure; n = 50); and 2) the Butenhoff et al. (2012a) study did not report incidences for pancreatic islet cell neoplasms. The first factor resulted in statistical dilution of tumor incidence in the high-dose group as many of the tumor types observed in the study, including hepatocellular neoplasms, were not reported until approximately 70 weeks of treatment or later. Therefore, the EPA conducted a re-analysis that excluded animals sacrificed at the interim time point from statistical analyses as it was biologically implausible for the 10 animals from the interim time point to have presented with neoplasms. The second factor impacted the EPA from recognizing the statistically significant trend in a second tumor site/type (pancreatic islet cell carcinomas) observed in the chronic cancer bioassay. As a result of identifying the second tumor site/type, PFOS does meet an additional characteristic for the designation of *Likely to Be Carcinogenic to Humans:* "an agent that has tested positive in animal experiments in more than one species, sex, strain, **site**, or exposure route, with or without evidence of carcinogenicity in humans" (emphasis added) (USEPA, 2005).

Overall, the Thomford/Butenhoff et al. (2012a; 2002) report, along with plausible associations between PFOS exposure and carcinogenicity reported in epidemiological studies, provides substantive evidence that PFOS exceeds the designation of *Suggestive Evidence of Carcinogenic Potential* and is consistent with *Likely Evidence of Carcinogenic Potential in Humans* (see Section 3.5.5 of the *Final Human Health Toxicity Assessment for PFOS* (USEPA, 2024d) for more information on the *Likely* determination). See Table D below for specific details on how PFOS exceeds the examples supporting the *Suggestive Evidence of Carcinogenic Potential* cancer descriptor in the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005).

After reviewing the examples of the descriptor *Carcinogenic to Humans*, the EPA has determined that at this time, the evidence supporting the carcinogenicity of PFOS does not warrant a descriptor exceeding *Likely to Be Carcinogenic to Humans*. The *Guidelines* indicate that a chemical agent can be deemed *Carcinogenic to Humans* if it meets <u>all</u> of the following conditions:

- "there is strong evidence of an association between human exposure and either cancer or the key precursor events of the agent's mode of action but not enough for a causal association, and
- there is extensive evidence of carcinogenicity in animals, and
- the mode(s) of carcinogenic action and associated key precursor events have been identified in animals, and
- there is strong evidence that the key precursor events that precede the cancer response in animals are anticipated to occur in humans and progress to tumors, based on available biological information" (USEPA, 2005).

As discussed in the subsection above, convincing epidemiological evidence supporting a causal association between human exposure to PFOS and cancer are currently lacking. Additionally, though the available evidence indicates that there are positive associations between PFOS and multiple cancer types, there is uncertainty regarding the identification of carcinogenic MOA(s) and associated key precursor events for PFOS in animals. See Table D below for specific details on how PFOS does not align with the examples supporting the *Carcinogenic to Humans* cancer descriptor in the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005).

Table D. Comparison of the PFOS Carcinogenicity Database with Cancer Descriptors as Outlined in the Guidelines for Carcinogen Risk Assessment (USEPA, 2005)

Comparison of Evidence for Suggestive and Carcinogenic Cancer Descriptors	
Suggestive Evidence of Carcinogenic Potential	
"A small, and possibly not statistically significant, increase in tumor incidence observed in a single animal or human study that does not reach the weight of evidence for the descriptor "Likely to Be Carcinogenic to Humans." The study generally would not be contradicted by other studies of equal quality in the same population group or experimental system" (USEPA, 2005)	**PFOS data exceed this description**. Observed statistically significant increases in hepatic tumors (adenomas in males and adenomas and carcinomas in females) at the high dose and a statistically significant trend overall in both sexes.
"A small increase in a tumor with a high background rate in that sex and strain, when there is some but insufficient evidence that the observed tumors may be due to intrinsic factors that cause background tumors and not due to the agent being assessed." (USEPA, 2005)	**This description is not applicable to the tumor types observed after PFOS exposure.**
"Evidence of a positive response in a study whose power, design, or conduct limits the ability to draw a confident conclusion (but does not make the study fatally flawed), but where the carcinogenic potential is strengthened by other lines of evidence (such as structure-activity relationships)." (USEPA, 2005)	**PFOS data exceed this description**. The study from which carcinogenicity data are available was determined to be *high* confidence during study quality evaluation.
"A statistically significant increase at one dose only, but no significant response at the other doses and no overall trend." (USEPA, 2005)	**PFOS data exceed this description**. Observed statistically significant increases in hepatic tumors (adenomas in males and adenomas and carcinomas in females) at the high dose and a statistically significant trend overall. Also observed statistically significant trend of increased pancreatic islet cell carcinomas with increasing dose.
Carcinogenic to Humans	
"This descriptor is appropriate when there is convincing epidemiologic evidence of a causal association between human exposure and cancer." (USEPA, 2005)	**PFOS data are not consistent with this description.** There is evidence of a plausible association between PFOS exposure and cancer in humans, however, the database is limited, there is uncertainty regarding the potential confounding of other PFAS, and there is limited mechanistic information that could contribute to the determination of a causal relationship.
Or, this descriptor may be equally appropriate with a lesser weight of epidemiologic evidence that is strengthened by other lines of evidence. It can be used when *all* of the following conditions are met:	

Comparison of Evidence for Suggestive and Carcinogenic Cancer Descriptors	
"There is strong evidence of an association between human exposure and either cancer or the key precursor events of the agent's MOA but not enough for a causal association." (USEPA, 2005)	**PFOS data are not consistent with this description.** There is evidence of an association between human exposure and cancer, however, there is limited mechanistic information that could contribute to the determination of a causal relationship.
"There is extensive evidence of carcinogenicity in animals." (USEPA, 2005)	**PFOS data are not consistent with this description.** Only one chronic cancer bioassay is available for PFOS. The database would benefit from *high* confidence chronic studies in other species and/or strains.
"The mode(s) of carcinogenic action and associated key precursor events have been identified in animals." (USEPA, 2005)	**PFOS data are not consistent with this description.** A definitive MOA has not been identified for each of the PFOS-induced tumor types identified in rats.
"There is strong evidence that the key precursor events that precede the cancer response in animals are anticipated to occur in humans and progress to tumors, based on available biological information." (USEPA, 2005)	**PFOS data are not consistent with this description.** The animal database does not provide significant clarity on the MOA(s) of PFOS in animals.

Notes: MOA = mode of action.

4 MCLG Derivation

4.1 PFOA

Consistent with the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005), the EPA reviewed the weight of evidence and determined that PFOA is *Likely to Be Carcinogenic to Humans* because "the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor *Carcinogenic to Humans.*" This determination is based on the evidence of kidney and testicular cancer in humans and LCTs, PACTs, and hepatocellular tumors in rats as described in Section 3.1 above, and Section 3.5 of the *Final Human Health Toxicity Assessment for PFOA* (USEPA, 2024e).

Consistent with the statutory definition of MCLG, the EPA establishes MCLGs of zero for carcinogens classified as either *Carcinogenic to Humans* or *Likely to Be Carcinogenic to Humans* where there is a proportional relationship between dose and carcinogenicity at low concentrations or where there is insufficient information to determine that a carcinogen has a threshold dose below which no carcinogenic effects have been observed. In these situations, the EPA takes the health protective approach of assuming that carcinogenic effects should therefore be extrapolated linearly to zero (USEPA, 2005). This is called the linear default extrapolation approach and ensures that the MCLG is set at a level where there are no anticipated adverse health effects, allowing for an adequate margin of safety (USEPA, 2016c, 1991, 1985). Here, the EPA has determined that PFOA is *Likely to Be Carcinogenic to Humans* based on sufficient evidence of carcinogenicity in humans and animals. The EPA has also determined that a linear default extrapolation approach is appropriate as there is no evidence demonstrating a threshold level of exposure below which there is no appreciable cancer risk (USEPA, 2005) and therefore, there is no known threshold for carcinogenicity. Based upon a consideration of the best available peer-reviewed science and data collected by accepted or best available methods, as well as the statutory directive to set the MCLG "at the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety," the EPA has finalized an MCLG of zero for PFOA in drinking water.

4.2 PFOS

Consistent with the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005), the EPA reviewed the weight of evidence and determined that PFOS is *Likely to Be Carcinogenic to Humans* because "the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor *Carcinogenic to Humans.*" This determination is based on the evidence of hepatocellular tumors in male and female rats, which is further supported by recent evidence of hepatocellular carcinoma in humans (Cao et al., 2022; Goodrich et al., 2022), pancreatic islet cell carcinomas in male rats, and mixed but plausible evidence of bladder, prostate, kidney, and breast cancers in humans as described in Section 3.2 above, and Section 3.5 of the *Final Human Health Toxicity Assessment for PFOS* (USEPA, 2024d).

Consistent with the statutory definition of MCLG, the EPA establishes MCLGs of zero for carcinogens classified as either *Carcinogenic to Humans* or *Likely to Be Carcinogenic to Humans* where there is a proportional relationship between dose and carcinogenicity at low concentrations or where there is insufficient information to determine that a carcinogen has a

threshold dose below which no carcinogenic effects have been observed. In these situations, the EPA takes the health protective approach of assuming that carcinogenic effects should therefore be extrapolated linearly to zero (USEPA, 2005). This is called the linear default extrapolation approach and ensures that the MCLG is set at a level where there are no anticipated adverse health effects, allowing for an adequate margin of safety (USEPA (1985); USEPA (1991); USEPA (2016c); *See* S. Rep. No. 169, 104*th* Cong., 1*st* Sess. (1995) at 3). Here, the EPA has determined that PFOS is *Likely to Be Carcinogenic to Humans* based on sufficient evidence of carcinogenicity in humans and animals. The EPA has also determined that a linear default extrapolation approach is appropriate as there is no evidence demonstrating a threshold level of exposure below which there is no appreciable cancer risk (USEPA, 2005) and therefore, there is no known threshold for carcinogenicity. Based upon a consideration of the best available peer-reviewed science and data collected by accepted or best available methods, as well as the statutory directive to set the MCLG "at the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety," the EPA has finalized an MCLG of zero for PFOS in drinking water.

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